STUDIO ADOPT: QUALI INDICAZIONI PER IL PAZIENTE ANZIANO?

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DIPARTIMENTO DI GERIATRIA E MALATTIE DEL METABOLISMO – SUN - NAPOLI

DIABETES RISK FACTORS IN AGEING

Decreased physical activity

Increased adiposity

Age effects on insulin action

Medication

Genetics

Coexisting illness

Age effects on Beta cells

→ INSULIN RESISTANCE

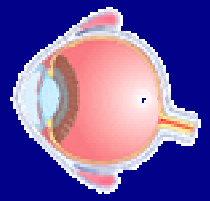
→ DECREASED INSULIN SECRETION

Impaired adaptation No ↑ insulin

Progression to IGTand type 2 diabetes

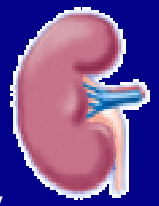
Chang AM, Am J Physiol Endocrinol Metab 284: E7–E12, 2003;

Type 2 diabetes is NOT a mild disease



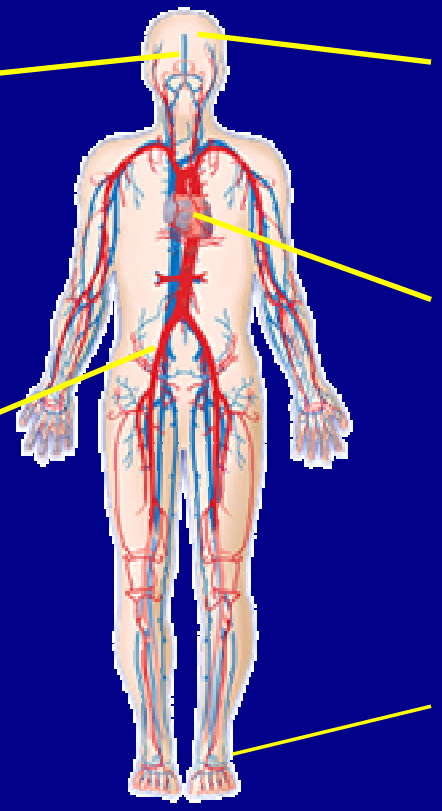
Diabetic retinopathy

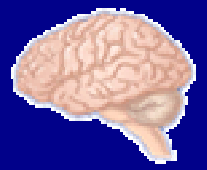
Leading cause of blindness in working-age adults[1]



Diabetic nephropathy

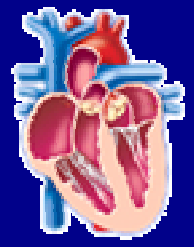
Leading cause of end-stage renal disease[2]





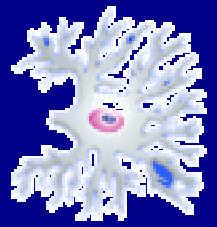
Stroke

1.2- to 1.8-fold increase in stroke[3]



Cardiovascular disease

75% diabetic patients die from CV events[4]

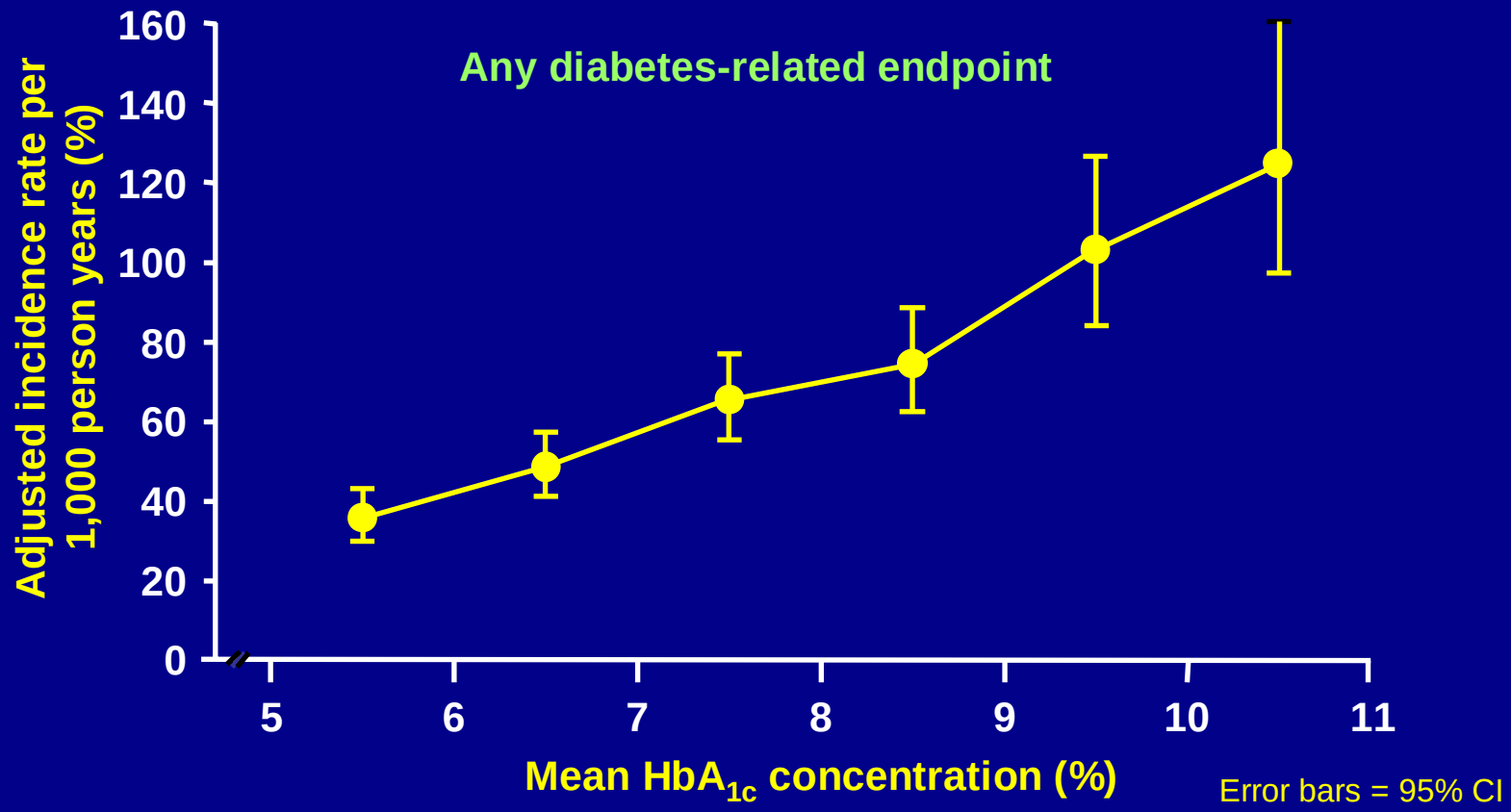


Diabetic neuropathy

Leading cause of non-traumatic lower extremity amputations[5]

[1]Fong DS, *et al. Diabetes Care* 2003;26 (Suppl. 1):S99–S102. [2]Molitch ME, *et al. Diabetes Care* 2003;26 (Suppl. 1):S94–S98. [3]Kannel WB, *et al. Am Heart J* 1990;120:672–676. [4]Gray RP & Yudkin JS. In *Textbook of Diabetes* 1997. [5]Mayfield JA, *et al. Diabetes Care* 2003;26 (Suppl. 1):S78–S79.

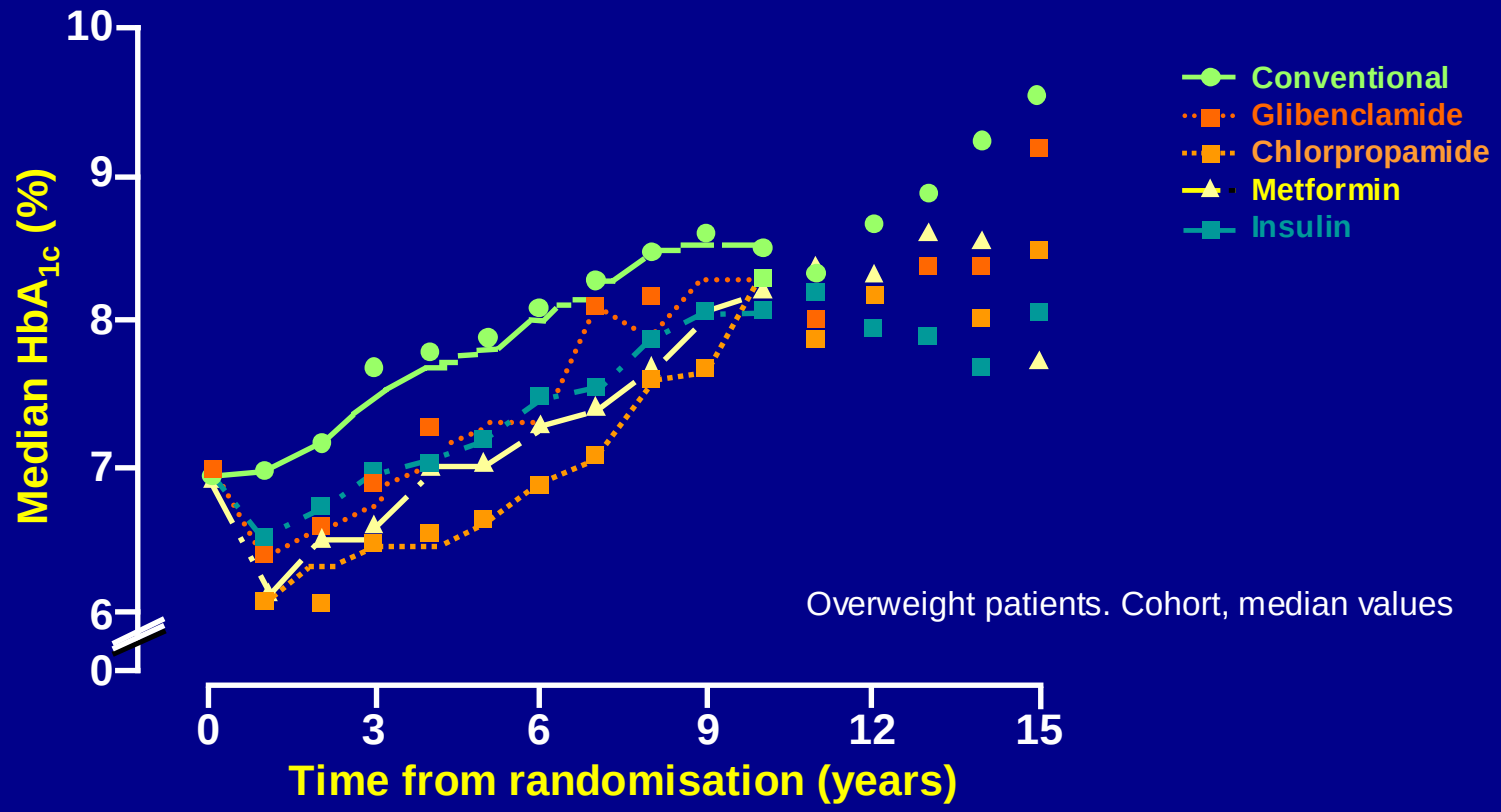
UKPDS: Correlation of HbA_{1c} concentration with rates of diabetic complications



Adjusted for age, sex and ethnic group; expressed for white males, aged 50–54 at diagnosis, mean duration of diabetes of 10 years

Adapted from Stratton IM, *et al.* UKPDS 35. *BMJ* 2000;321:405–412.

The UKPDS demonstrated loss of glycaemic control with all agents studied



n	0 years	5 years	10 years	15 years
Conventional	411	309	200	22
Glibenclamide	277	229	148	18
Chlorpropamide	285	202	129	11
Metformin	342	279	181	21
Insulin	409	327	199	20

Adapted from UKPDS Group. UKPDS 34. *Lancet* 1998;352:854–865.

What about Thiazolidinediones?

- Reduce glucose levels in type 2 diabetes
- Increase insulin sensitivity
- Delay/prevent diabetes in high risk subjects
- May preserve beta-cell function

ADOPT

A Diabetes Outcome Progression Trial

ADOPT

A Diabetes Outcomes Progression Trial

An international, long-term, double-masked, randomised clinical trial to evaluate whether the thiazolidinedione rosiglitazone provides more durable and safe glycaemic control than the biguanide metformin or the sulphonylurea glyburide (glibenclamide)

Inclusion Criteria

- Type 2 diabetes mellitus ≤3 years
- Drug naïve
- Male and female
- Aged 30–75 yr inclusive
- Fasting plasma glucose

  126–180 mg/dl (7–10 mmol/l) after 4-week run-in and prior to randomisation

Exclusion Criteria

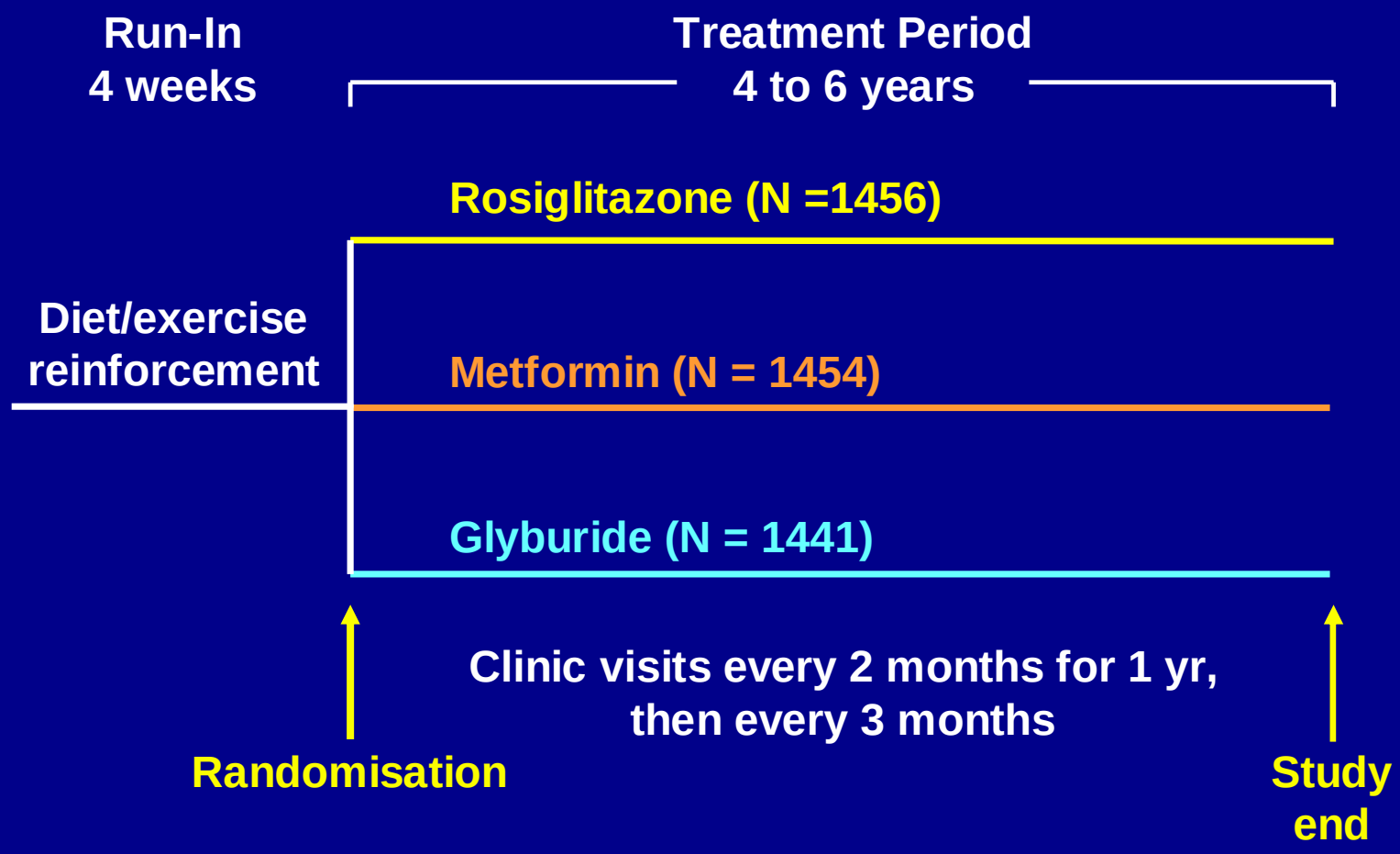
- Previous use of glucose-lowering therapy
- Women of child-bearing potential
- Significant hepatic disease, renal impairment
- Unstable or severe angina
- Congestive heart failure (NYHA Class I–IV)
- Uncontrolled hypertension

Dose Titration

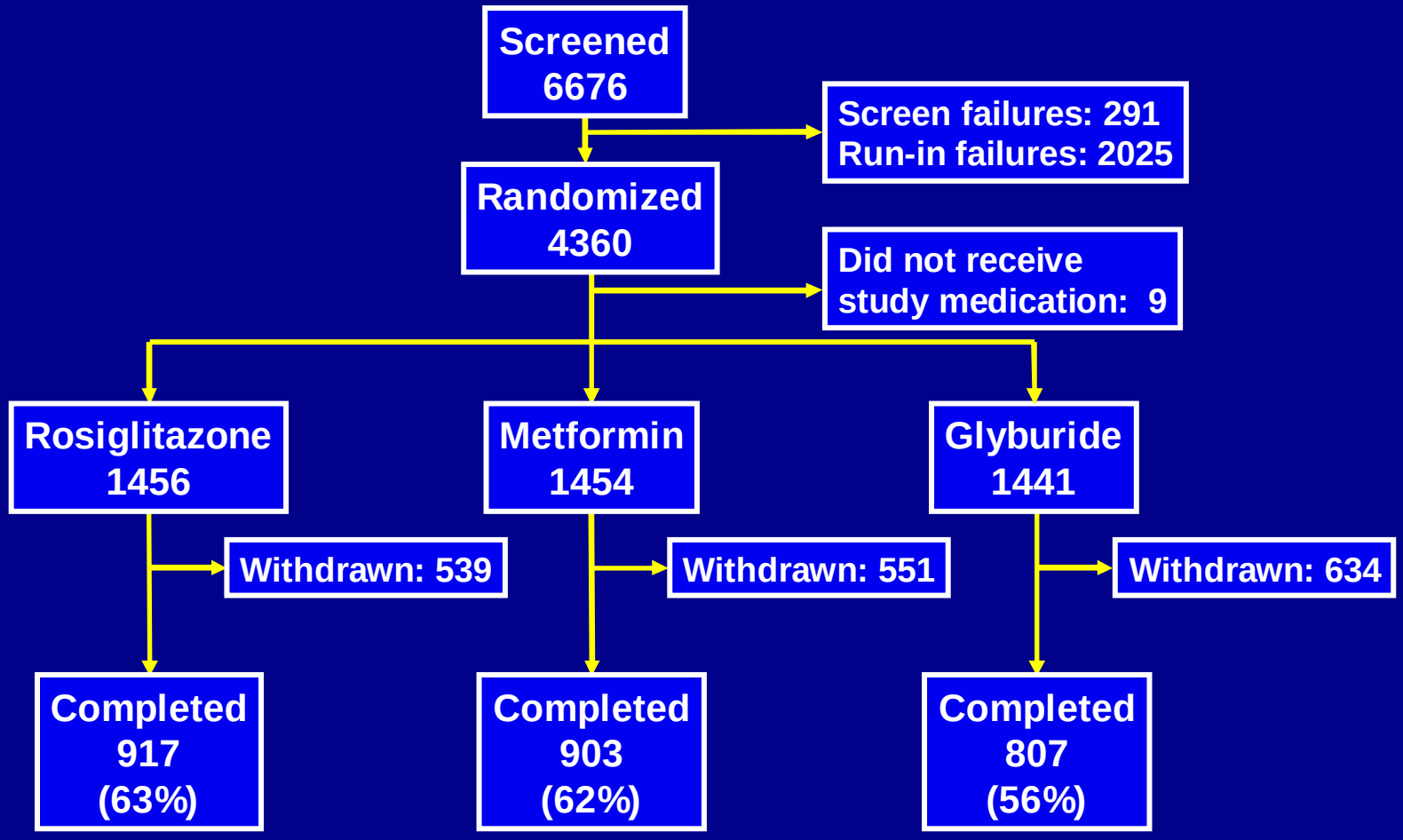
	Initial	Maximal
Rosiglitazone	4 mg od	4 mg bid
Metformin	500 mg od	1 g bid
Glyburide	2.5 mg od	7.5 mg bid

Double-masked over-encapsulated drugs

ADOPT Design



Patient Disposition



Baseline Characteristics

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Age, yr	56.3 ± 10.0	57.9 ± 9.9	56.4 ± 10.2
Male	56%	59%	58%
Caucasian	87%	89%	89%
North America	52%	52%	53%
Europe	48%	48%	47%

P>0.05 for all comparisons

Baseline Characteristics

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Time since diabetes diagnosis			
<1 yr	45%	46%	44%
1–2 yr	52%	50%	52%
>2–3 yr	3%	4%	4%
Hypertension Rx	51%	51%	52%
Lipid-lowering Rx	26%	26%	26%
History of CVD	16%	19%	17%

P>0.05 for all comparisons

Baseline Characteristics

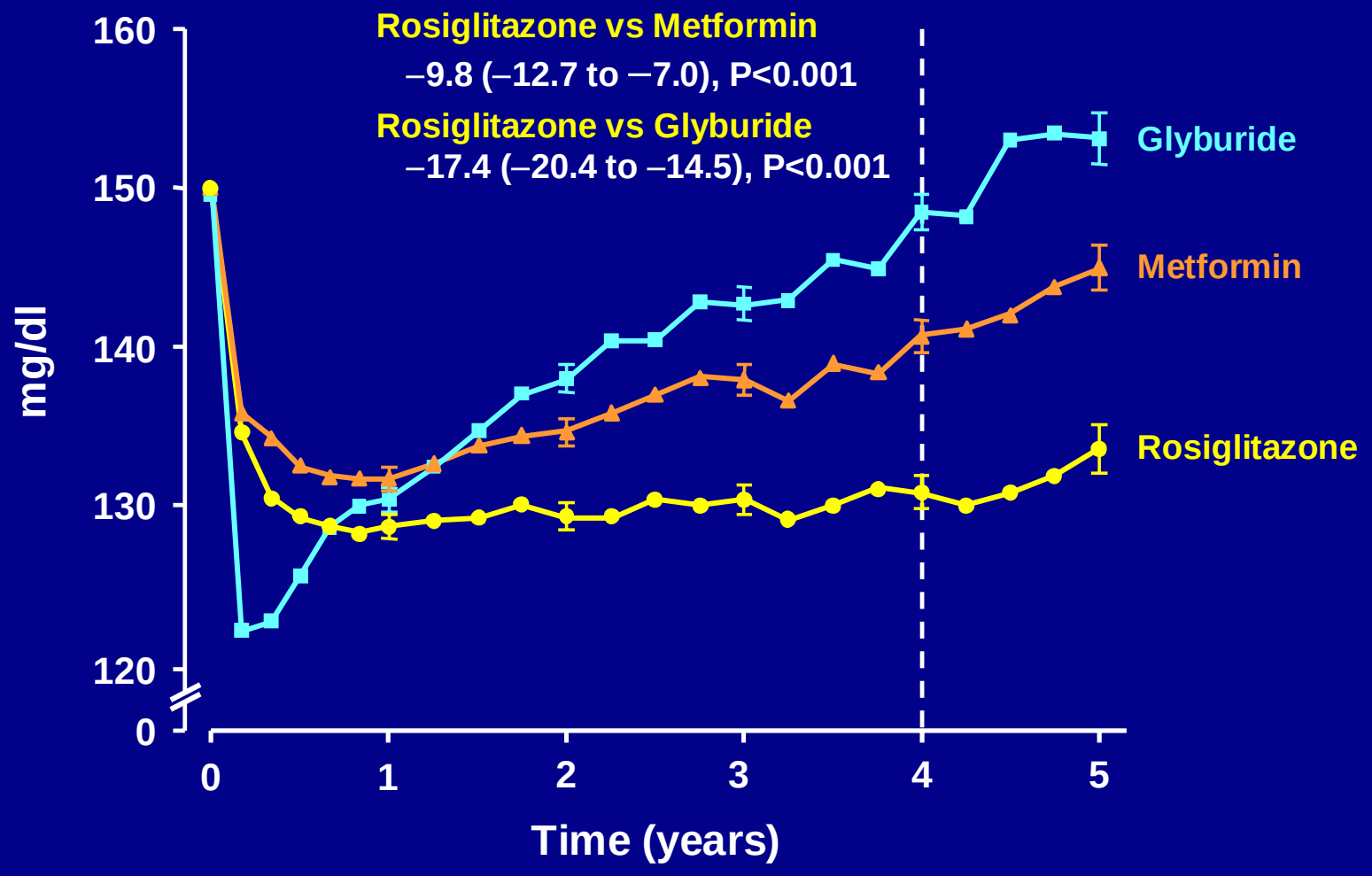
	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
BMI (kg/m^2)	32.2 ± 6.7	32.1 ± 6.1	32.2 ± 6.3
FPG (mg/dl)	152 ± 26	151 ± 26	152 ± 27
HbA1c (%)	7.4 ± 0.9	7.4 ± 0.9	7.4 ± 0.9

P>0.05 for all comparisons

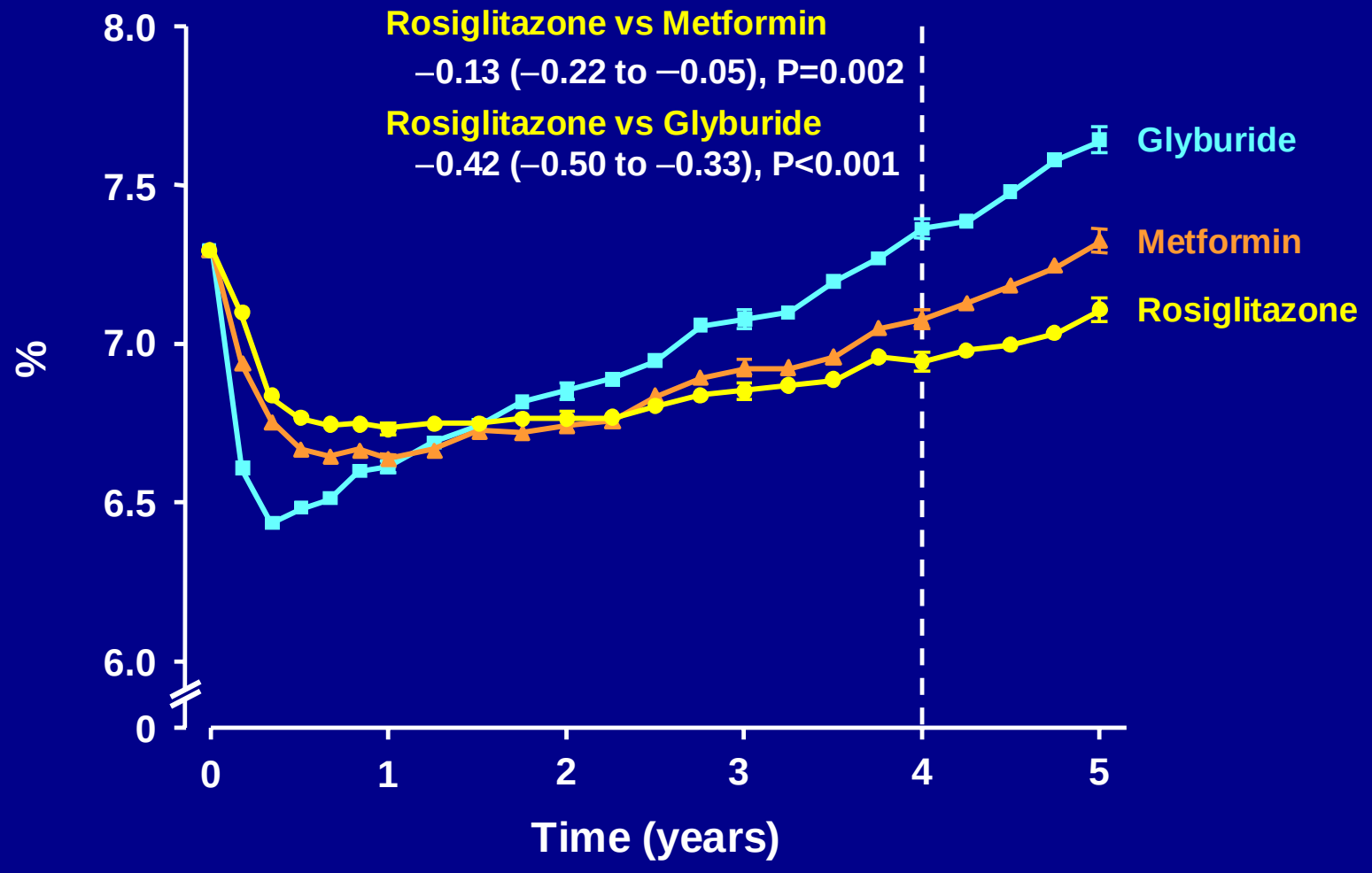
Primary Outcome

Monotherapy Failure

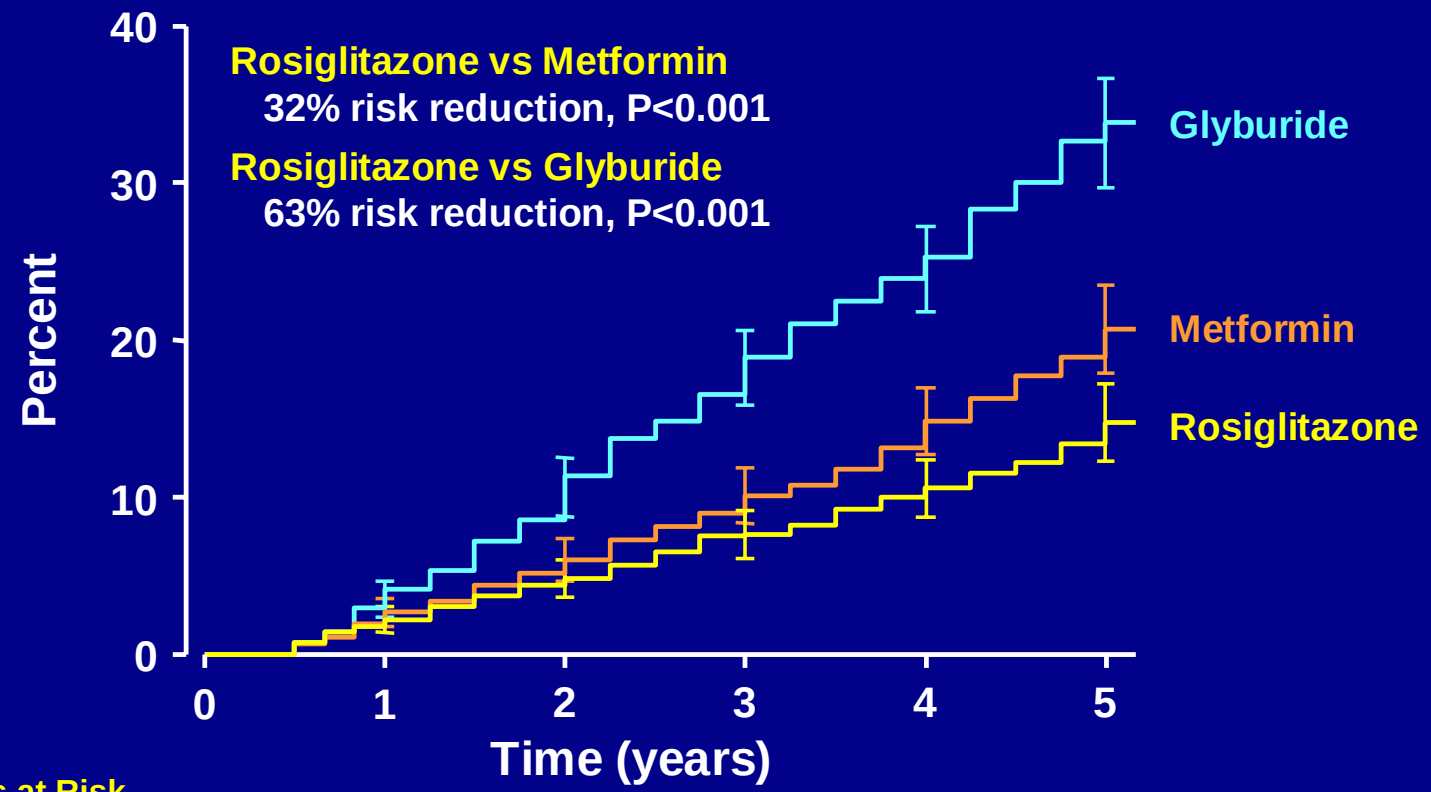
Fasting Plasma Glucose Over Time



HbA1c Over Time



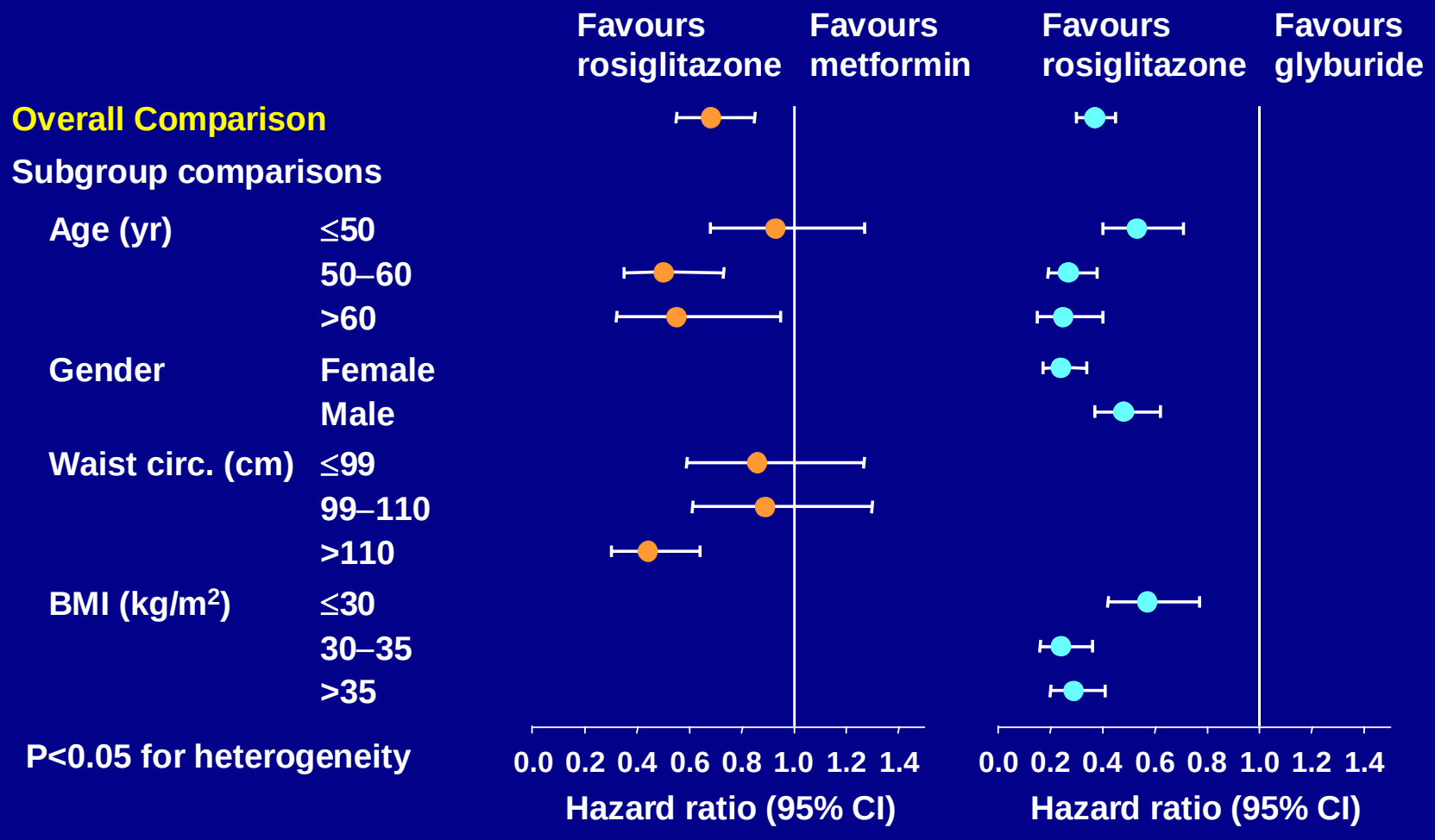
Cumulative Incidence of Monotherapy Failure (FPG >180 mg/dl)



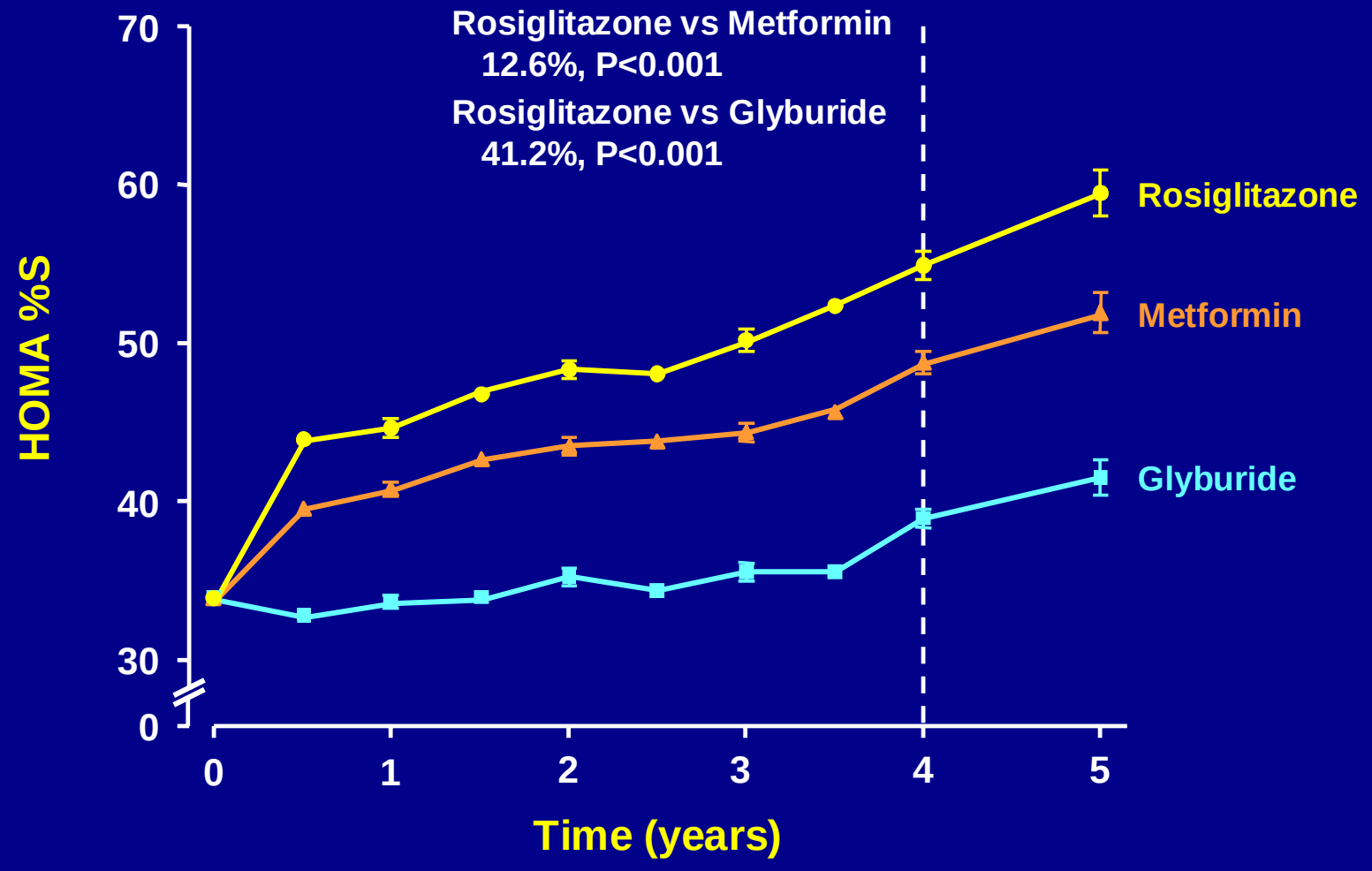
Patients at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

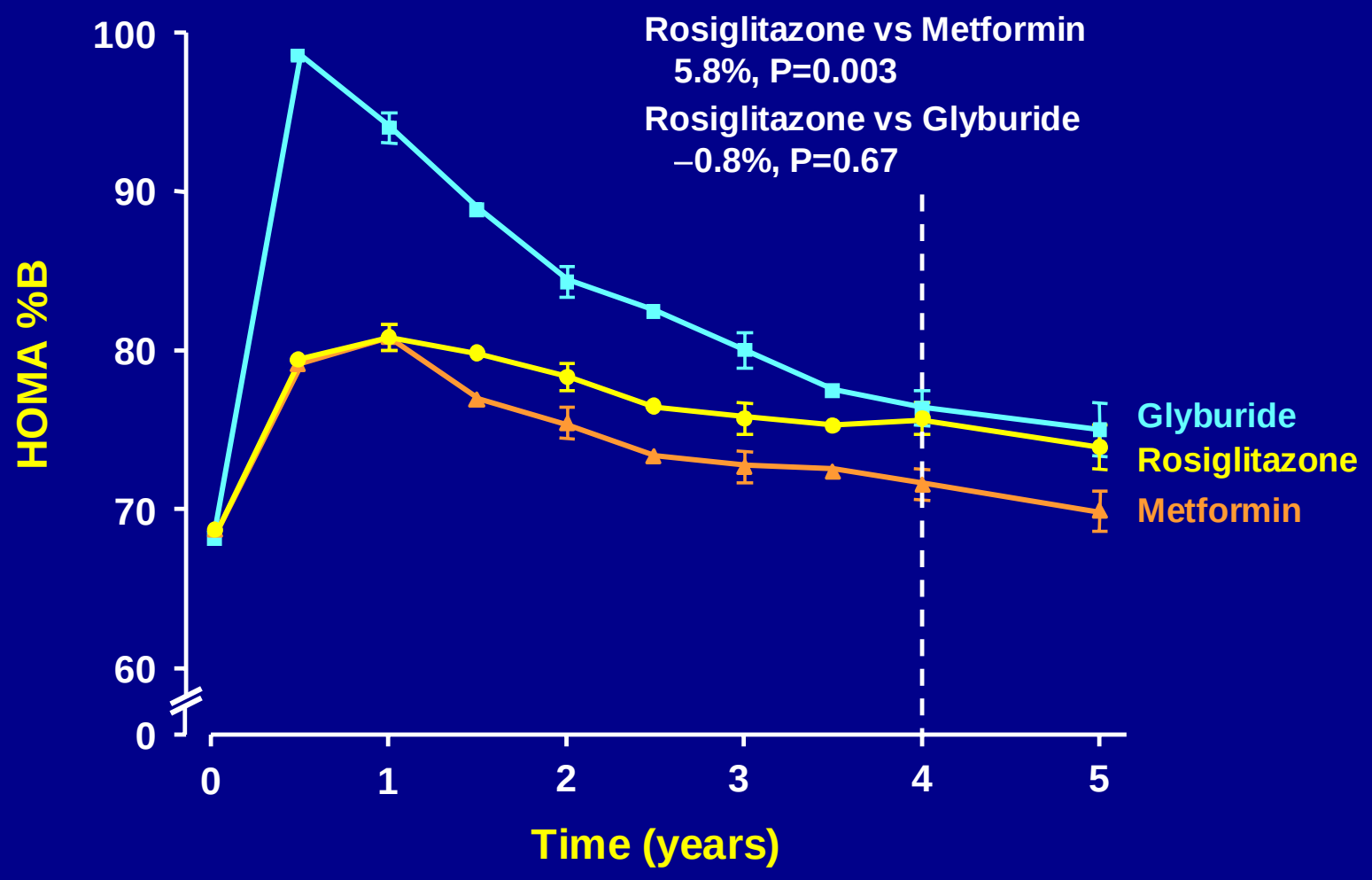
Monotherapy Failure Subgroup Heterogeneity



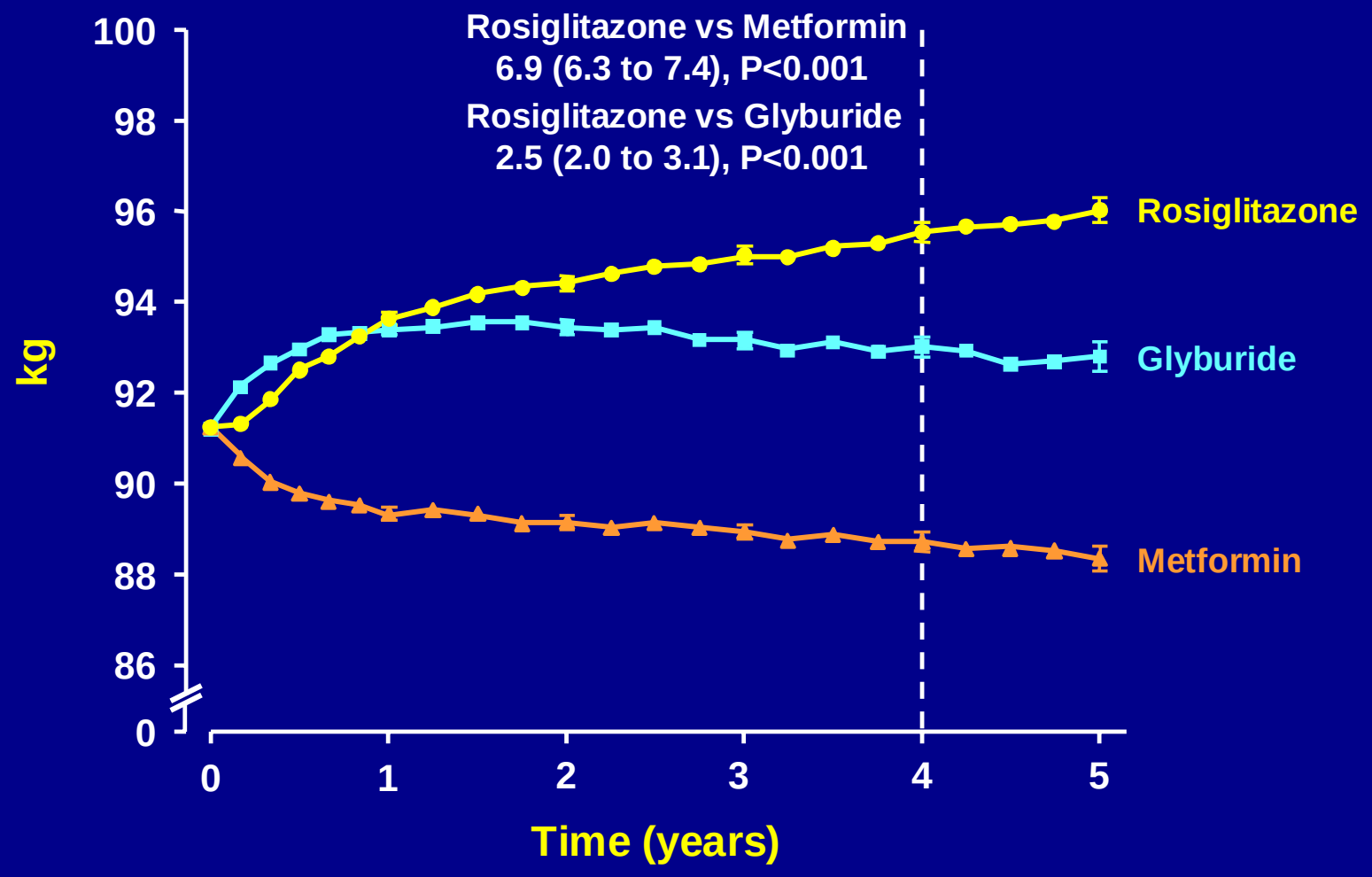
Insulin Sensitivity Over Time



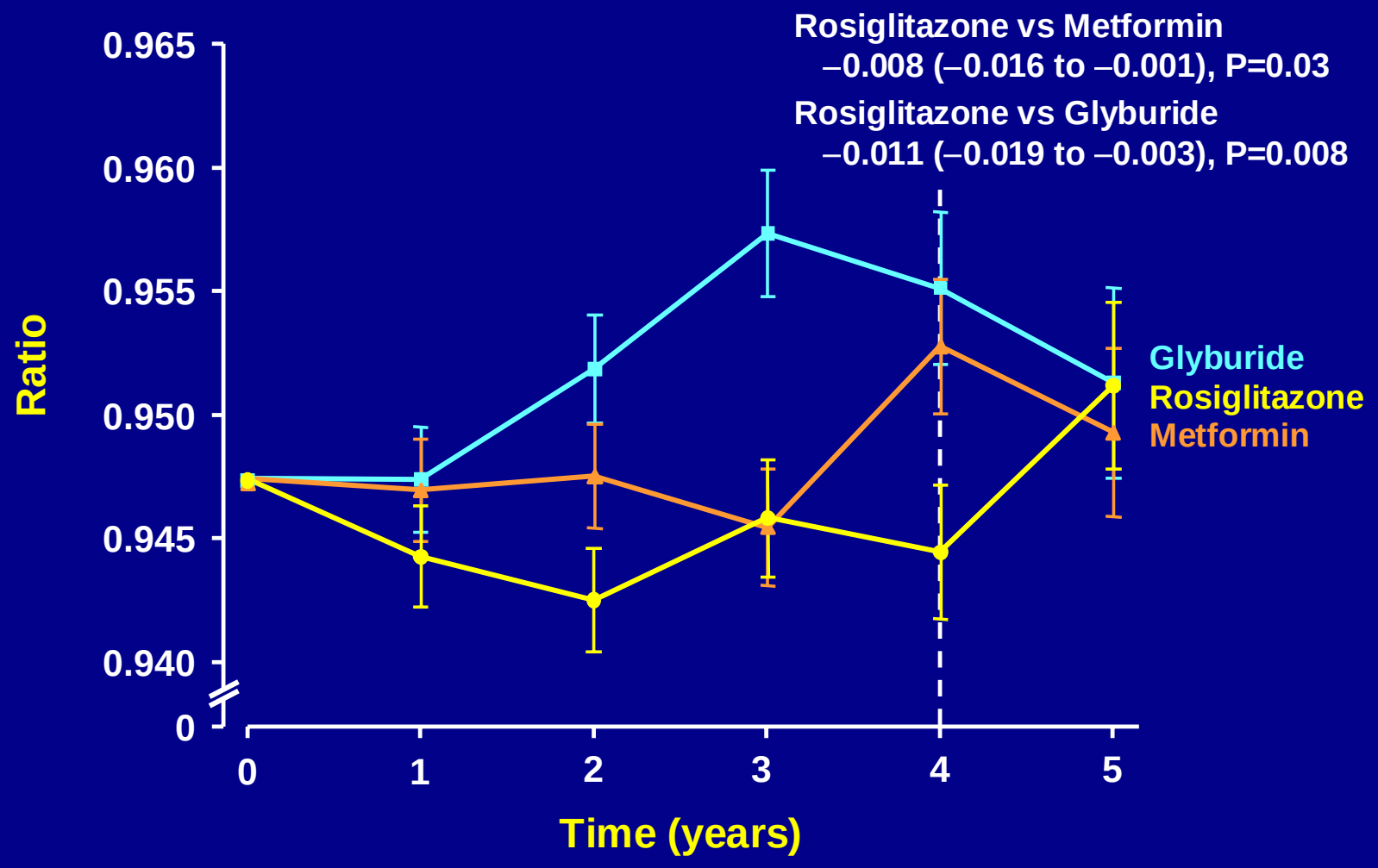
Beta-cell Function Over Time



Weight Over Time



Waist-hip Ratio Over Time



ADOPT Safety Data

Adverse Events, Hospitalizations and Deaths

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Patients with event(s), n (%)	1338 (92%)	1341 (92%)	1321 (92%)
Hospitalization from any cause			
Patients, n (%)	169 (12%)	172 (12%)	150 (10%)
Events, n	251	267	203
Death from any cause, n (%)	34 (2.3%)	31 (2.1%)	31 (2.2%)

Vascular Serious Adverse Events: Investigator Reported

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Cardiovascular disease, n (%)	49 (3.4%)	46 (3.2%)	26 (1.8%)
Myocardial infarction			
Fatal, n (%)	2 (0.1%)	2 (0.1%)	3 (0.2%)
Non-fatal, n (%)	22 (1.5%)	18 (1.2%)	11 (0.8%)
CHF, n (%)	12 (0.8%)	12 (0.8%)	3 (0.2%)
Stroke, n (%)	13 (0.9%)	17 (1.2%)	12 (0.8%)
Peripheral vascular disease, n (%)	7 (0.5%)	6 (0.4%)	4 (0.3%)

P<0.05 vs. rosiglitazone

Congestive Heart Failure

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Adverse events, n (%)	22 (1.5%)	19 (1.3%)	9 (0.6%)
Serious adverse events, n (%)	12 (0.8%)	12 (0.8%)	3 (0.2%)
Cardiologist review, n (%)	9 (0.6%)	8 (0.6%)	4 (0.3%)

P<0.05 vs. rosiglitazone

Other Adverse Events

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Gastrointestinal, n (%)	335 (23%)	557 (38%)	316 (22%)
Weight gain, n (%)	100 (7%)	18 (1%)	47 (3%)
Hypoglycaemia, n (%)	142 (10%)	168 (12%)	557 (39%)
Oedema, n (%)	205 (14%)	104 (7%)	123 (9%)

P<0.05 vs. rosiglitazone

Fractures

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Men , n (%)	32 (4.0%)	29 (3.4%)	28 (3.4%)
Women , n (%)	60 (9.3%)	30 (5.1%)	21 (3.5%)
Upper limb, n (%)	22 (3.4%)	10 (1.7%)	9 (1.5%)
Lower limb , n (%)	36 (5.6%)	18 (3.1%)	8 (1.3%)
Hip, n (%)	2 (0.3%)	2 (0.3%)	0 (0.0%)
Spine, n (%)	1 (0.2%)	1 (0.2%)	1 (0.2%)

P<0.05 vs. rosiglitazone

Laboratory Measures

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
ALT, IU/L (95% CI)	21.4 (20.6–22.2)	24.9 (24.1–25.8)	27.2 (26.3–28.1)
ALT >3x ULN, n (%)	14 (1.0%)	16 (1.1%)	11 (0.8%)
Haematocrit, % (95% CI)	40.6 (40.4–40.8)	41.6 (41.4–41.8)	41.6 (41.4–41.8)
Haematocrit ≥5% below ref. range, n (%)	41 (2.8%)	22 (1.5%)	14 (1.0%)

P<0.05 vs. rosiglitazone

Il Rosiglitazone e' indicato nel paziente anziano?

SI perché :

- I dati scorporati per età evidenziano un effetto positivo sul controllo metabolico specie oltre i 60 anni.
- Ha effetti piu' duraturi sul controllo metabolico nei confronti della metformina e della glibenclamide
- Riduce la possibilità di evitare gravi ipoglicemie

Il Rosiglitazone e' indicato nel paziente anziano?

No perché :

- Può aggravare lo scompenso cardiaco congestizio
- Può causare fratture spontanee nelle donne in post-menopausa
- CHD?

Il Rosiglitazone e' indicato nel paziente anziano?

Allora ? E indicato nella seguente tipologia di pazienti:

- Età >60 anni
- Preferibilmente maschi in sovrapeso o obesi
- Donne non affette e/o non a rischio di osteoporosi
- Comunque dopo aver escluso la presenza di CHF e/o CHD